

# Safety and ethics of bronchoscopy and endobronchial biopsy in difficult asthma

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## Abstract

**Aim**—To investigate the safety of bronchoscopy and endobronchial biopsy in children with difficult asthma, and discuss the ethical issues associated with the procedure.

**Methods**—A three year prospective observational study was performed in two tertiary paediatric respiratory centres specialising in the management of children with difficult asthma. A total of 48 children with difficult asthma and 35 non-asthmatic children were studied.

**Results**—Flexible bronchoscopy was performed under general anaesthesia in 38 children with difficult asthma, and rigid bronchoscopy was performed in 10, following a two week course of prednisolone. Endobronchial biopsy was performed in 47 patients. Perioperative complications occurred in one asthmatic undergoing flexible bronchoscopy (desaturation) and in two undergoing rigid bronchoscopy (desaturation in one, and bronchospasm and desaturation in one). There were no cases of significant bleeding or pneumothorax among the asthmatics. Flexible bronchoscopy was performed in 35 non-asthmatic patients with a variety of clinical indications. The total number of perioperative complications was greater in the non-asthmatics undergoing flexible bronchoscopy than in the asthmatics (17 complications in 35 children versus one in 38). Fever requiring hospital admission was documented in two asthmatics following bronchoscopy. Four asthmatics reported an increase in symptoms in the week following bronchoscopy.

**Conclusions**—Bronchoscopy and endobronchial biopsy under general anaesthesia can be performed safely in children with difficult asthma, when the bronchoscopist and anaesthetist are suitably trained. The procedure is acceptable to the families involved.

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Some children, with a proven diagnosis of asthma, continue to suffer from worrying morbidity despite high dose treatment, even after intensive efforts to diagnose and treat coexisting disorders, optimise treatment adherence, and reduce the level of exposure to aggravating factors.<sup>1 2</sup> Current asthma guidelines recommend the use of regular oral corticosteroids for

children with such severe asthma.<sup>3</sup> This may improve asthma control, but at the risk of adverse effects, particularly growth failure and adrenal suppression. Other treatments, including cyclosporin, methotrexate, intravenous immunoglobulin, or a continuous subcutaneous infusion of terbutaline, may therefore be tried.<sup>4–7</sup> Each is associated with potentially serious adverse effects and/or a labour intensive regimen. Currently there is little information to help clinicians select the most effective therapy for the individual.

We, and others, have previously recommended that patients who respond poorly to corticosteroids, particularly those in whom unconventional therapies are being considered, should undergo bronchoscopy and endobronchial biopsy.<sup>8–10</sup> This allows direct inspection of the airways and the opportunity for examination of the underlying pathology. Different phenotypes of difficult asthma appear to exist,<sup>11–14</sup> and it seems logical to tailor treatment according to information obtained from bronchoscopic evaluation. Biopsy evidence of steroid resistant eosinophilic inflammation in a symptomatic child, accompanied by the typical structural features of basement membrane thickening and increased smooth muscle, confirms the clinical impression of severe asthma, and strengthens the argument for the use of further anti-inflammatory therapy, such as cyclosporin.<sup>4</sup> Conversely, the absence of the typical pathological features of asthma should lead to a reappraisal of the diagnosis or consideration of therapies aimed at targets other than inflammation, such as a continuous subcutaneous infusion of terbutaline.<sup>6</sup>

For this approach to become accepted, it must be shown to be safe and acceptable to parents and children. This report describes our experience of bronchoscopy and endobronchial biopsy in children with difficult asthma, focusing on the safety and the ethical issues raised. The pathological findings will be described in future reports.

## Methods

### SUBJECTS

#### Patients

We studied children with difficult asthma<sup>15</sup> who attended the Royal Brompton Hospital (RBH) and the Royal London Hospital (RLH) between 1997 and 1999 (table 1). All patients underwent a full conventional assessment.<sup>1 2 16</sup> Difficult asthma was defined as follows: children with asthma, with symptoms requiring a rescue bronchodilator on at least three days per week, despite treatment with at least 1600 µg/day of inhaled budesonide (or equivalent),

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Table 1 Clinical characteristics of children with difficult asthma and non-asthmatic control group

	Asthmatic	Non-asthmatic
Number	48	35
Age (y)	10.9 (4–17)	9.6 (5–15)*
FEV <sub>1</sub> (% predicted) (n = 45)	79 (44–104)	
Inhaled budesonide (mg/day) (n = 15)	2.0 (0.8–3.2)	
Inhaled fluticasone (mg/day) (n = 32)	1.6 (1.0–3.0)	
Inhaled beclomethasone (mg/day) (n = 1)	1.5	
Number on long acting $\beta_2$ agonists	40/48	
Number on oral prednisolone	18/48	
Other drugs (currently used or previously tried)	Theophylline 11/48 Montelukast 7/48 Cyclosporin 2/48 CSIT† 2/48 Cromoglycate 1/48 IVIG‡ 1/48	

Data are expressed as mean (range) or proportions (out of 48).

\*Not significant.

†Continuous subcutaneous infusion of terbutaline.

‡Intravenous immunoglobulin.

Table 2 Clinical indications for flexible bronchoscopy in non-asthmatic children

Indication	Number
Chronic cough/recurrent infection	12
Stridor/upper airway obstruction	6
Cystic fibrosis	5
Bronchiectasis	3
Infection in the immunocompromised	3
Haemoptysis	2
Cough following TOF* repair	2
Interstitial lung disease	1
Unexplained shadowing on chest x ray	1
Total	35

\*Tracheo-oesophageal fistula.

as well as regular long acting  $\beta_2$  agonists (or a previous unsuccessful trial of long acting  $\beta_2$  agonists), and/or regular prednisolone.<sup>11</sup>

#### Non-asthmatic control group

We studied 35 age matched children undergoing flexible bronchoscopy for other clinical indications (tables 1 and 2).

#### ETHICS APPROVAL

Bronchoscopy and biopsy were performed as part of the clinical assessment of children with difficult asthma. The primary aim was to examine the airway pathology in order to guide management for the individual. Endobronchial biopsy provided information about the degree and nature of inflammation, as well as structural features, such as basement membrane thickness and smooth muscle mass. An additional benefit was the ability to investigate the mechanisms of difficult asthma in children. Approval was obtained from the ethics committees of both hospitals for use of biopsy material for research studies investigating airway inflammation, remodelling, and corticosteroid responsiveness. Informed consent was obtained from the parents of children who took part in these studies.

#### STUDY PROTOCOL

Asthmatic patients underwent bronchoscopy following a two week course of prednisolone (2 mg/kg/day, maximum dose 40 mg/day). Prednisolone was given in order to determine whether the child had true steroid resistant asthma, and to assess whether this was associated with persistent airway inflammation.

Adherence to prednisolone was assessed by simultaneous measurement of serum prednisolone and cortisol, using high performance liquid chromatography.<sup>12 17</sup> Additionally, the treatment aimed to maximise the safety of the procedure. Non-asthmatic patients did not receive prednisolone before bronchoscopy.

#### ANAESTHESIA

Bronchoscopy was performed in theatre under general anaesthesia, administered by a consultant anaesthetist or specialist registrar under consultant supervision, with a trained operating department assistant. Salbutamol (5 mg via nebuliser) was given to asthmatic patients 30 minutes before induction of anaesthesia. If used, premedication with atropine or glycopyrrolate was given. Intravenous access was obtained in all children. Anaesthesia was induced with intravenous (propofol) or volatile (sevoflurane) agents, and maintained with volatile agents (isoflurane, sevoflurane, or halothane) or intravenous propofol. Carrier gases were oxygen, oxygen/air mixture, or oxygen/nitrous oxide mixture. The choice of muscle relaxant, if used, was between vecuronium, atracurium, rocuronium, or mivacurium. The minimum monitoring included continuous ECG recording and measurements of oxygen saturation, end tidal carbon dioxide, and non-invasive blood pressure. Additional corticosteroid cover was not routinely given. If upper airway pathology, tracheomalacia, or other causes of airway compression were suspected,<sup>18</sup> the initial examination was performed during flexible bronchoscopy with the patient breathing spontaneously and the bronchoscope passed through a face mask or laryngeal mask. Further examination, and subsequent procedures, were performed via a face mask, laryngeal mask, or endotracheal tube. A size two or three laryngeal mask or 6.5 mm endotracheal tube was needed to allow adequate ventilation around the bronchoscope. Ventilation was assisted manually, if necessary. During rigid bronchoscopy, the airway was maintained using the bronchoscope. If indicated, airway dynamics were first assessed with the patient breathing spontaneously, before the administration of muscle relaxants. Following bronchoscopy, muscle relaxation was reversed using neostigmine and glycopyrrolate.

#### FLEXIBLE BRONCHOSCOPY

Flexible bronchoscopy was performed at the Royal Brompton Hospital. Non-asthmatic patients were bronchoscoped by one of three consultant respiratory paediatricians, using a size 3.6 mm or 4.9 mm external diameter bronchoscope (Olympus, UK). All patients with difficult asthma were bronchoscoped by the same consultant (AB), using a 4.9 mm external diameter bronchoscope with a 2.2 mm suction channel (Olympus, UK). Bronchoalveolar lavage (BAL) was performed in the right middle lobe, using 10–40 ml aliquots of normal saline, to a maximum of 80 ml. Endobronchial biopsy specimens (up to six) were taken from the subcarinae of the right lower lobe, using cupped forceps (FB-19C-1, Olym-

pus, UK). Each set of forceps was used on a maximum of five patients.

#### RIGID BRONCHOSCOPY

Rigid bronchoscopy was performed at the Royal London Hospital by a consultant paediatric surgeon (DM). A size 3.5, 4.0, or 5.0 bronchoscope was used. BAL was performed as for flexible bronchoscopy. Up to six endobronchial biopsy specimens were taken from the main carina and the carina between the right middle and lower lobes, using punch biopsy forceps. The same set of forceps was used for all patients.

#### POSTOPERATIVE CARE

Patients were nursed in the theatre recovery area, with oxygen given by facemask until fully awake. They were then observed on the ward for at least four hours. Oxygen saturation, temperature, heart rate, and respiratory rate were measured every 15 minutes for the first hour, every 30 minutes for the next hour, and hourly subsequently. Chest radiography was not performed routinely. Before discharge children were examined by a clinician. Spirometry was not performed. Patients not normally on regular oral corticosteroids discontinued prednisolone following bronchoscopy. Those taking regular prednisolone as maintenance treatment, had the dose tapered to the maintenance dose. Biopsy/lavage results and subsequent management were discussed at outpatient follow up. At this visit parents and children were asked whether there had been any increase in symptoms following bronchoscopy.

#### STATISTICAL ANALYSIS

Data were tested for normality using histograms and Kolmogorov–Smirnov testing. Normally distributed data are expressed as mean

(range). The age of the asthmatic and the non-asthmatic groups was compared using unpaired *t* testing. For the two groups undergoing flexible bronchoscopy, the number of complications was compared using  $\chi^2$  testing. A *p* value less than 0.05 was considered statistically significant.

#### Results

Flexible bronchoscopy was performed in 38 children with difficult asthma, and rigid bronchoscopy was performed in 10 (table 1). One family refused to allow their child to undergo bronchoscopy. One family did not give their child prednisolone before bronchoscopy. Table 3 shows details of the anaesthetic and bronchoscopic procedures.

Few perioperative complications occurred among the patients with difficult asthma (table 3). Desaturation occurred on three occasions and was managed by increasing the inspired oxygen and removing the bronchoscope. One episode of desaturation during rigid bronchoscopy was accompanied by bronchospasm, managed, in addition to the above measures, by changing the volatile agent from isoflurane to halothane. There was no significant bleeding and no clinical or radiological instances of pneumothorax. Comparing the two groups undergoing flexible bronchoscopy, there were more perioperative complications in the non-asthmatic group than in the asthmatic group (17 complications in 35 children versus one in 38, *p* < 0.01), in particular, laryngospasm and apnoea. Postoperatively, two asthmatic children developed a fever of above 38.5°C several hours after the procedure. One remained in hospital overnight; the other was discharged, but readmitted to his local hospital the next day. BAL subsequently grew *Streptococcus pneumoniae* and he remained in hospital for several days. Four asthmatic children reported an increase in symptoms and use of rescue bronchodilator for several days following bronchoscopy (flexible in three; rigid in one).

#### Discussion

We consider our report shows that bronchoscopy with BAL and endobronchial biopsy can be performed safely in children with difficult asthma under general anaesthesia, and that the procedure is acceptable to parents and children.

This is the largest series of its kind to have been reported. However, we accept that the number of patients is still small, and that there will always be the potential for morbidity and mortality, however minimal, when performing this procedure. It is important to emphasise that the procedure was undertaken at two centres specialising in the management of children with difficult asthma, by experienced personnel. Although flexible bronchoscopy can be performed under conscious sedation,<sup>19</sup> we find general anaesthesia more satisfactory. Use of general anaesthesia almost always ensures that the procedure can be completed successfully with minimal discomfort to the child. In experienced hands the risks of general anaesthesia for a child are very small, and the procedure

Table 3 Details of anaesthetic and bronchoscopic (flexible and rigid) procedures in asthmatic and non-asthmatic patients

	Difficult Rigid (n = 10)	Asthma Flexible (n = 38)	Non-asthma Flexible (n = 35)
Induction of anaesthesia			
Intravenous	10	33	19
Inhalational	0	5	16
Maintenance of anaesthesia			
Intravenous	0	2	0
Inhalational	10	35	33
Both	0	1	2
Muscle relaxant used	10	31	13
Type of airway used			
Face mask	N/A	3	16†‡
Laryngeal mask	N/A	8*	8
Intubated	N/A	28*	14†‡
Bronchoscopic procedures			
Bronchoalveolar lavage	5	38	32
Endobronchial biopsy	10	37	3
Complications			
Laryngospasm	0	0	7
Bronchospasm	1	0	0
Apnoea	0	0	4
Desaturation§	2	1	6
Bradycardia	0	0	0
Bleeding	0	0	0
Pneumothorax	0	0	0
Total	3	1¶	17¶

Data are expressed as absolute numbers.

\*Includes one patient intubated electively following initial examination via a laryngeal mask.

†Includes two patients intubated electively following initial examination via a face mask.

‡Includes one patient intubated as an emergency following initial examination via a face mask.

§ More than 10% fall below baseline oxygen saturation.

¶*p* < 0.01.

can usually be performed as a day case. In a much larger series, routine use of endobronchial biopsy as an additional clinical procedure was without complications.<sup>20</sup>

For flexible bronchoscopy, there were more perioperative complications in the non-asthmatic group than in the asthmatic group. This may be because the asthmatic patients were more likely to be intubated and to have received muscle relaxants. In these patients characterisation of the extent and pattern of airway inflammation was the main purpose of bronchoscopy, rather than assessment of the upper airway and airway dynamics, which was performed more often in the non-asthmatic group. Bronchospasm, which may have been expected to be a significant problem in the asthmatics, was encountered only once during rigid bronchoscopy. The low incidence of complications in the asthmatic group may also be related to the preoperative course of prednisolone. In addition to maximising the safety of the procedure, this, coupled with evidence of satisfactory adherence, allowed us to determine whether there was true steroid resistant eosinophilic inflammation.

Few children reported problems following bronchoscopy. Fever was documented in two patients. This may have occurred in other patients following discharge, but was not reported by parents at follow up. Four patients reported an increase in symptoms in the week following bronchoscopy. We acknowledge that ideally patients should have performed spirometry following the procedure, with a period of peak expiratory flow (PEF) monitoring at home. However, the majority of children had completed a two week PEF diary before bronchoscopy, and we recognise the possibility of diary fatigue.<sup>21</sup> A study of adult asthmatics revealed no difference in PEF rates for two weeks before and after flexible bronchoscopy.<sup>22</sup> In general the response from the families involved was positive, with most parents grateful for the information provided, particularly if this led to a more logical plan of management. However, this procedure will only be ethical, as well as safe, if it is subsequently shown to contribute to individual patient management.

In this small group of children with difficult asthma, bronchoscopy, BAL, and endobronchial biopsy was performed safely under general anaesthesia, following a two week course of prednisolone, when performed by trained, experienced personnel. These studies

should improve our understanding of the pathology of difficult asthma, with the development of more rational prescribing.

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- 1 Balfour-Lynn IM. Difficult asthma: beyond the guidelines. *Arch Dis Child* 1999;**80**:201-6.
- 2 Connet G. Paediatric evaluation of difficult asthma. *Eur Respir Rev* 2000;**10**:40-4.
- 3 The British Thoracic Society, The National Asthma Campaign, The Royal College of Physicians of London in association with the General Practitioner in Asthma Group, the British Association of Accident and Emergency Medicine, the British Paediatric Respiratory Society, and the Royal College of Paediatrics and Child Health. The British Guidelines on Asthma Management 1995. Review and Position Statement. *Thorax* 1997;**52**:S1-21.
- 4 Coren ME, Rosenthal M, Bush A. The use of cyclosporin in corticosteroid dependent asthma. *Arch Dis Child* 1997;**77**:522-3.
- 5 Guss S, Portnoy J. Methotrexate treatment of severe asthma in children. *Pediatrics* 1992;**89**:635-9.
- 6 O'Driscoll BRC, Ruffles SP, Ayres JG, Cochrane GM. Long term treatment of severe asthma with subcutaneous terbutaline. *Br J Dis Chest* 1988;**82**:360-7.
- 7 Vrugt B, Wilson S, van Velzen E, et al. Effects of high dose intravenous immunoglobulin in two severe corticosteroid insensitive asthmatic patients. *Thorax* 1997;**52**:662-4.
- 8 Payne DNR, Hubbard M, McKenzie SA. Corticosteroid unresponsiveness in asthma: primary or acquired? *Pediatr Pulmonol* 1998;**25**:59-61.
- 9 Thomas PS, Geddes DM, Barnes PJ. Pseudo-steroid resistant asthma. *Thorax* 1999;**54**:352-6.
- 10 Adelroth E. Evaluation of difficult asthma: bronchial biopsies and bronchoalveolar lavage. *Eur Respir Rev* 2000;**10**:36-9.
- 11 ERS Taskforce on difficult/therapy-resistant asthma. Difficult/Therapy-Resistant Asthma: the need for an integrated approach to define clinical phenotypes, evaluate risk factors, understand pathophysiology and find novel therapies. *Eur Respir J* 1999;**13**:1198-208.
- 12 Payne DNR, Wilson NM, James A, et al. Evidence for different subgroups of difficult asthma in children. *Thorax* (in press).
- 13 Wenzel SE, Schwartz LB, Langmack EL et al. Evidence that severe asthma can be divided pathologically into two inflammatory subtypes with distinct physiologic and clinical characteristics. *Am J Respir Crit Care Med* 1999;**160**:1001-8.
- 14 Pavord ID, Brightling CE, Woltmann G, Wardlaw AJ. Non-eosinophilic corticosteroid unresponsive asthma. *Lancet* 1999;**353**:2213-14.
- 15 Warner JO, Götz M, Landau LI, et al. Management of asthma: a consensus statement. *Arch Dis Child* 1989;**64**:1065-79.
- 16 Lask B. Psychological factors. In: Silverman M, ed. *Childhood asthma and other wheezing disorders*. London: Chapman and Hall Medical, 1995:421-8.
- 17 Payne DNR. Adrenal response to glucocorticoid treatment. *Lancet* 2000;**355**:1458.
- 18 Payne DNR, Lincoln C, Bush A. Lesson of the week: right-sided aortic arch in children with persistent respiratory symptoms. *BMJ* 2000;**321**:687-8.
- 19 Tobias JD. Sedation and anesthesia for pediatric bronchoscopy. *Curr Opin Pediatr* 1997;**9**:198-206.
- 20 Bush A, Pohunek P. Brush biopsy and mucosal biopsy. *Am J Respir Crit Care Med* 2000;**162**:S18-22.
- 21 Redline S, Wright EC, Kattan M, et al. Short-term compliance with peak flow monitoring: results from a study of inner city children with asthma. *Pediatr Pulmonol* 1996;**21**:203-10.
- 22 Humbert M, Robinson DS, Assoufi B, et al. Safety of fibre-optic bronchoscopy in asthmatic and control subjects and effect on asthma control over two weeks. *Thorax* 1996;**51**:664-9.